

Drugs in the young - part 2

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Medicine in the Young (Part 2)

Maurice Hall and Lezley-Anne Hanna

Lecturer (Education) and Senior Lecturer (Education), respectively; Queen's University Belfast

After completing this part of the module you will:

- have an awareness of some statistics relating to medicines use in children
- appreciate the difference between the terms 'unlicensed' and 'off-label'
- be able to discuss the general principles that should apply when unlicensed or off-label medicines are prescribed
- know which over-the-counter (OTC) medicines are not suitable for use in children

Introduction

The previous article (Part 1) outlined the important pharmacokinetic characteristics in the developing child that need to be accounted for when using medicines in children. Having a fundamental knowledge of these pharmacokinetic factors is important in ensuring that medicines are used safely and effectively. This article (Part 2), aims to focus specifically on the use of medicines in children, looking particularly at factors pharmacists should consider when providing over-the-counter medicines for use in children.

Statistics

In England, those aged under 19 years were estimated to make up 22.5% of the population in 2015, while only being responsible for 4.5% of the total number of items dispensed. Conversely, those aged 60 and over, made up 23% of the population, but accounted for 60.4% of the items dispensed. Even though the young do account for proportionately less medicine use, they have distinctive characteristics that make them an important group to consider. Furthermore, there are many over-the-counter (OTC) medicines available for use in children and in Britain in 2015, OTC sales of paediatric analgesics totalled £83.5 million.

Medicine use

Prescribing medicines for children

The prescribing of medicines for children has historically been difficult due to the lack of information regarding the use of medicines in children. In order to get a licence to promote the use of a medicine in children, the manufacturer has to conduct clinical trials that involve children; these can prove difficult and there are a number of ethical issues that have to be considered. Hence, it is relatively common for **unlicensed** or **off-label** medicines to be used in the young.

- Unlicensed medicines are medicines that do not have a UK marketing authorisation and are not expected to acquire one in the next 2 years
- Off-label medicines are medicines with existing UK marketing authorisations that are used outside the terms of their marketing authorisation, for example, by indication, dose, route or patient population and are not expected to get a marketing authorisation to cover this use in the next 2 years

When medicines are being prescribed for any patient in an unlicensed or off-label context, the prescriber should ensure that:

- No alternative appropriately licensed medicine exists
- There is sufficient evidence or experience of using the medicine to know it is safe and effective
- They take responsibility for prescribing the medicine and overseeing the patient's care, including monitoring and follow-up
- They record the medicine being prescribed and the rationale for prescribing it

The process should involve patient or carer input and information regarding the treatment, including possible adverse effects, should be given so they can make an informed decision. It should be noted that doctors, dentists, independent nurse prescribers, independent pharmacist prescribers and supplementary prescribers can all prescribe unlicensed medicines or use off-label medicines, whereas optometrists, therapeutic radiographers, physiotherapists and podiatrists who are independent prescribers are not permitted to prescribe unlicensed medicines but may prescribe medicines off-label.

A number of medicines should be avoided in children or should be used with caution given the increased potential for adverse reactions or toxicity. Examples of such drugs are shown in Table 1.

Table 1 Medicines with notable effects in children (see also Table 2 for OTC medicines)

Antihistamines (sedating) – children are more susceptible to side-effects. Can rarely cause paradoxical excitement. Use in the latter part of the third trimester may cause adverse effects in neonates such as irritability, paradoxical excitability, and tremor
Arachis oil (for treatment of scalp conditions) – best avoided in children under 5
Benzyl benzoate – avoid in children due to its irritant nature
Chloramphenicol – avoid in neonates due to risk of Grey syndrome
Corticosteroids - long-term use in prepubertal children can cause growth suppression
Danazol – avoid in children due to androgenic effects
Glibenclamide – avoid in children due to increased risk of hypoglycaemia
Iron – children are at increased risk of iron toxicity, with iron preparations being an important cause of accidental overdose in children
Lamotrigine – can cause severe skin reactions, especially in children
Phenobarbital – can cause paradoxical hyperactivity in children
Sodium valproate – where possible, avoid in children under 2 (especially if taking other antiepileptics)
Sulphonamide antibiotics – risk of kernicterus due to displacement of bilirubin from binding sites on plasma albumin
Tetracyclines – avoid in children under 12 due to enamel hypoplasia and permanent discolouration of the teeth

OTC medicines

As previously stated, there is a plethora of OTC medicines available for use in children. However, there are also many instances when OTC medicines are not suitable for children or when guidance has been released about specific OTC medicines. It is important to have up-to-date knowledge of this area given that a fundamental responsibility of the community pharmacist relates to the safe and effective use of medicines, including OTC medicines. Table 2 outlines conditions or OTC medicines associated with

particular guidance (and also provides examples of key groups of medicines that should be avoided in children).

Table 2 Over-the-counter (OTC) medicines with particular guidance in relation to use in children (or examples of key groups of medicines that should be avoided)

Subject area	Medicines associated with guidance/key groups of medicines to be avoided
Respiratory	<p><i>Medicines and Healthcare products Regulatory Agency (MHRA) guidance on cough and cold products</i> https://www.gov.uk/drug-safety-update/over-the-counter-cough-and-cold-medicines-for-children</p> <p>Following a scientific review of the evidence about 7 or 8 years ago, cough and cold ingredients such as pseudoephedrine, ephedrine, guaifenesin, pholcodine are not suitable for use in under 6 years because the risks (side-effect profile) outweighs the benefits. Many of these products lack a robust evidence-base.</p> <p><i>Current best practice for managing cough and colds in children aged under 6 years:</i> Simple measures such as ensuring your child has plenty to drink and gets enough rest will help. Paracetamol or ibuprofen can also be used to reduce temperature (see other fever guidance below). Nasal saline may help thin and clear nasal secretions. Child >1 year, a warm drink of lemon and honey may help to ease a cough. No better after about 5 days, ask a healthcare professional for advice.</p> <p><i>Current best practice for managing cough and colds in children aged 6-12 years:</i> OTC cough and cold medicines can be considered after basic principles of best care have been tried (see above). Treatment should be restricted to 5 days or less. Care should be taken to give the correct dose. Children should not be given more than one cough or cold preparation at a time because different brands may contain the same active ingredient. NB The MHRA guidance on cough and cold products only applies to products that have licensed indications for cough and cold. For example, chlorphenamine is on their restricted list but when it is in Piriton® it is okay to sell to children over 1 year. Piriton® is licensed for hay fever and other allergies (including itchy skin rash of chickenpox) but has no indication for cough and cold.</p> <p><i>Honey:</i> is not suitable under 12 months of age (infant botulism risk). http://www.nhs.uk/conditions/pregnancy-and-baby/pages/foods-to-avoid-baby.aspx</p> <p><i>Codeine:</i> Previous MHRA advice (2010) stated that over-the-counter oral liquid medicines containing codeine should no longer be used to treat cough in children and young people under 18 years. In addition, all over-the-counter oral liquid codeine medicines were to be supplied in child-resistant containers. http://www.mhra.gov.uk/home/groups/spar/documents/websiteresources/con096798.pdf</p> <p>However, in 2015, the MHRA issued the following guidance about codeine in cough and cold products: "Do not use codeine in children under 12 as it is associated with a risk of respiratory side effects. Codeine is not recommended for adolescents (12 to 18) who have problems with breathing". https://www.gov.uk/drug-safety-update/codeine-for-cough-and-cold-restricted-use-in-children</p> <p>Oral <i>echinacea</i> herbal products: the MHRA issued guidance on this a few years ago (2012) not recommended for use in under 12 years (allergic reactions). http://webarchive.nationalarchives.gov.uk/20141205150130/http://www.mhra.gov.uk/NewsCentre/Pressreleases/CON180627</p> <p><i>See NICE pathway on self-limiting respiratory tract infections</i> https://pathways.nice.org.uk/pathways/self-limiting-respiratory-tract-infections---antibiotic-prescribing</p> <p><i>Allergic rhinitis:</i> OTC corticosteroid intranasal preparations are usually not suitable for use in under 18 years https://www.medicines.org.uk/emc/medicine/14212 https://www.medicines.org.uk/emc/medicine/21565</p>

Women's Health	<p>Cystitis remedies: while products may be licensed for use in children, best practice centres on referral for further investigation (rather than recommending OTC products). Uncomplicated cystitis is not common in children so could be a structural abnormality, urinary tract infection or abuse. See also NICE pathway on urinary tract infections in children and young people. https://www.nice.org.uk/guidance/qs36</p> <p>Vaginal candidiasis (thrush): refer under 16 years due to product licence restrictions</p> <p>OTC naproxen 250mg tablets for primary dysmenorrhoea are licensed for 15-50 years</p> <p>OTC tranexamic acid 500mg tablets for heavy menstrual bleeding are not licensed for use in under 18 years.</p> <p>OTC emergency contraception: Levonelle One Step– not for under 16 years whereas ellaOne manufacturer states it “is suitable for any woman of child bearing age, including adolescents.” (therefore appropriate legislation and pertinent guidance such as that provided by the Department of Health and pharmacy regulatory and professional bodies should be considered if recommending it to a patient under the legal age of consent to any form of sexual activity). https://www.medicines.org.uk/emc/medicine/15227 https://www.medicines.org.uk/emc/medicine/22280 See also: http://www.fpa.org.uk/factsheets/law-on-sex</p>
Gastro-intestinal	<p>Constipation – NICE pathway recommends that children have a physical examination done as part of the diagnosis stage. https://www.nice.org.uk/guidance/cg99?unlid=97695977201610274347</p> <p>Diarrhoea –NICE have published guidance on managing gastroenteritis (diarrhoea and vomiting) in children under 5 years, including an ‘assessing dehydration chart’ https://pathways.nice.org.uk/pathways/diarrhoea-and-vomiting-in-children</p> <p>OTC Proton pump inhibitors (omeprazole, esomeprazole, pantoprazole) tend to be not licensed for under 18 years whereas OTC H₂ antagonist (ranitidine) tend to not be licensed for under 16 years but this shouldn't be an issue given heartburn is not common in children (excluding reflux in babies)</p> <p>OTC loperamide is not suitable for use in under 12 years (care with Imodium products – must be 18 years+ to use it for acute episodes of diarrhoea linked to irritable bowel syndrome)</p> <p>Haemorrhoid preparations containing hydrocortisone such as Anusol® HC tend not to be licensed for use in under 18 years (Germaloids® HC spray is not for use in under 16 years). This shouldn't cause problems in practice since haemorrhoids are not common in children. https://www.medicines.org.uk/emc/medicine/8463 https://www.medicines.org.uk/emc/PL.21846.latest.pdf</p>
Travel	<p>Chloroquine dosing for antimalarial chemoprophylaxis: theoretical versus OTC product dosing may not align. If this is the case, refer patient to the doctor to be prescribed the appropriate dose rather than recommending the OTC product out of licence. [assuming that chloroquine is the appropriate choice in the first instance]</p>
Pain	<p>Paracetamol: age ranges and doses changed (2011), but not for safety reasons per se http://www.nhs.uk/news/2011/11November/Pages/new-child-calpol-paracetamol-doses.aspx</p> <p>Codeine is contra-indicated for use in under 12 years (toxicity risk) https://www.gov.uk/drug-safety-update/codeine-for-analgesia-restricted-use-in-children-because-of-reports-of-morphine-toxicity</p> <p>Aspirin is contra-indicated for use in under 16 years (Reye's syndrome risk) unless given under the advice of a doctor. This also applies to oral salicylates such as choline salicylate and bismuth subsalicylate.</p> <p>OTC sumatriptan is only for 18-65 age range</p>
Ear	<p>Acute otitis media (AOM) – follow NICE guidance regarding offering simple analgesia for pain relief and fever (paracetamol or ibuprofen) and providing the correct information on immediate versus delayed antibiotic prescribing, given that many cases resolve without the need for antibiotics.</p>

	http://cks.nice.org.uk/otitis-media-acute#!scenario Otitis externa: OTC Earcalm (acetic acid 2%) is indicated for the treatment of superficial infections of the external auditory canal but is not suitable for use in under 12 years https://www.medicines.org.uk/emc/medicine/17298
Eye	Topical OTC chloramphenicol may not be licensed for use in under 2 years, depending on the specific manufacturer (one such example is Optrex® Bacterial Conjunctivitis 1% w/w Eye ointment) https://www.medicines.org.uk/emc/medicine/32184 However, Brolene® Antibiotic 1.0% w/w Eye Drops SPC states to “talk to your doctor before giving this medicine to a newborn infant. Dosage adjustment may be necessary.” https://www.medicines.org.uk/emc/medicine/30103
Mouth	Daktarin sf 2% oral gel for oral thrush has an age limit (4 months) due to choking risk. However, it is also contra-indicated in those whose swallowing reflex is not sufficiently developed. https://www.medicines.org.uk/emc/medicine/22032 Some chlorhexidine-containing mouthwashes have an age limit of 12 years (unless recommended by your dentist) https://www.medicines.org.uk/emc/PIL.24660.latest.pdf
Skin	Be aware that the US Food and Drug Administration (FDA) has approved the first OTC retinoid treatment for acne (Adapalene – Differin® Gel 0.1%) in the US for patients aged 12 years and over. http://www.medscape.com/viewarticle/865918 . Topical corticosteroids such as HC45® cream (hydrocortisone acetate BP 1.0% w/w) are not licensed for use in under 10 years without medical advice. Other products such as Eumovate Eczema and Dermatitis Cream® (clobetasone butyrate 0.05 % w/w) are not for use in under 12 years without medical advice https://www.medicines.org.uk/emc/medicine/23417 https://www.medicines.org.uk/emc/medicine/16111 Lyclear Dermal Cream is indicated for the treatment of scabies in adults and children >2 months of age, and crab lice in adults. But the manufacturer also states: only limited experience is available with Lyclear Dermal Cream in children aged 2 months to 23 months. Therefore, treatment must be given only under close medical supervision in this age group. https://www.medicines.org.uk/emc/medicine/10439
Childhood conditions	Be familiar with NICE fever management (antipyretics such as paracetamol or ibuprofen not routinely advocated unless child is also distressed). See NICE for current guidance on alternating doses of ibuprofen and paracetamol. https://pathways.nice.org.uk/pathways/feverish-illness-in-children and how to recognise the signs of meningitis and sepsis http://www.nhs.uk/Conditions/Meningitis/Pages/Symptoms.aspx http://www.nhs.uk/conditions/Blood-poisoning/Pages/Introduction.aspx Post-immunisation pyrexia : care with OTC paracetamol license versus current guidance on paracetamol use in relation to the Meningitis B vaccine https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/483408/9413-paracetamol-menB-2page-A4-08-web.pdf Information about the UK childhood immunisation schedule is available: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/554298/Green_Book_Chapter_11.pdf Paracetamol: age ranges and doses changed (2011), but not for safety reasons per se http://www.nhs.uk/news/2011/11November/Pages/new-child-calpol-paracetamol-doses.aspx Ibuprofen is not suitable for pain or fever management in chickenpox (only paracetamol) due to potential increased risk of necrotising soft tissue infection and invasive group A streptococcal infections. http://www.gponline.com/chickenpox-varicella-zoster-clinical-review/infections-and-infestations/viral-infections/article/1284872

Conclusion:

Pharmacists are well placed to ensure medicine use in the young is safe, effective and, as much as is possible, evidence-based (regardless as to whether it is a prescribed or OTC medicine). Given the vulnerable nature of children with their distinctive physiology and age-related drug handling capabilities, it is important that all healthcare professionals, including pharmacists, ensure that the benefits of any medicine are not outweighed by the risks. Therefore, having a fundamental knowledge of pharmacokinetics in children (at various stages of childhood), coupled with utilising reliable evidenced-based resources and having a sound understanding of key pieces of legislation is essential. Future research should focus on expanding the evidence-base for unlicensed or off-label medicine use in children so that clinical decision-making is better informed.

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